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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,980	FEDER ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Finality of the previous Office Action is withdrawn herewith. This Non-Final Office Action is a reply to the "Amendment After Final Rejection" filed 29 August 2003 (hereinafter, 29 August Amendment) filed in response to the Final Office Action mailed 3 June 2003 (hereinafter 3 June Office Action). Claims 20-41 were considered in the 3 June Office Action. Claim 20 was amended in the 29 August Amendment. Claims 20-41 are pending and under consideration.

Response to Amendment

Claim Rejections - 35 USC § 112

Claims 20 and 30-41 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-41 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim Rejections - 35 USC § 102

Rejection of claims 20, 25, 28-30 and 38 under 35 U.S.C. 102(a) as being anticipated by NCBI ENTREZ ACCESSION NO: gi:10039473 evidenced by the notation in the first line of "COMMENT" is withdrawn.

Rejection of claims 20-26, 28-30 and 38 under 35 U.S.C. 102(b) as being anticipated by NCBI ENTREZ ACCESSION NO: gi:2133864 is withdrawn.

Response to Arguments

Claims 20 and 30-41 have been rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for reasons of record in the 3 June Office Action and the First Office Action on the Merits mailed 11 November 2002 (11 November Office Action). In the 29 August Amendment, Applicant first argues, the function of the claimed sequence has been established by the homology of the claimed sequence with other sequences. This argument has been full considered but is not found persuasive. Even if one were to accept, *arguendo*, that the nucleic acid sequence encoding a polypeptide set forth as SEQ ID NO: 2 has the asserted function, the disclosure does not provide adequate written description for the full scope of the claimed subject matter. As pointed out in the 11 November Office Action, "the ability of a DNA molecule to hybridize to another molecule or 70% identity is not a relevant identifying characteristic because the ability to hybridize or 70% identity at the nucleic acid level cannot be reliably correlated with the true function of the molecule (e.g. encode a protein or regulate expression of a gene)" (page 5). Thus, the specification does not adequately describe the relevant

identifying characteristics of the genus of nucleic acids that hybridize to, or have 70% identity with a disclosed polynucleotide and has the disclosed function.

Applicant next submits that coupled with the knowledge that the claimed sequence encodes a novel potassium channel beta subunit, one of ordinary skill in the art would readily appreciate certain substitutions that would provide a polynucleotide sequence consistent with the asserted function. Applicant states, "[a]fter considering the nature of a given substitution and the location in the primary nucleotide sequence of the substitution, one of ordinary skill in the art can eliminate much of the unpredictability the Patent Office suggests" (page 6). This argument is not persuasive because neither the specification nor the art disclose the structural determinants which dictate the functional characteristics of the polypeptide encoded by the instant claimed polynucleotide and, as pointed out in previous Office Actions, the effect of amino acid substitution on protein function is unpredictable. Therefore, the skilled artisan would not be able to distinguish polynucleotides that have the disclosed activity from polynucleotides that do not have the disclosed activity. Thus, the claims fail to meet the written description of 35 U.S.C. §112, first paragraph, because the specification does not disclose the claimed polynucleotides in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 20-41 have been rejected under 35 U.S.C. 112, first paragraph, as lacking an enabling disclosure. In the 29 August Amendment, Applicant argues that the Patent Offices rejection of the claims is narrowly focused on the lack of identity between human Maxi-K potassium channel beta subunit and the claimed sequence. Applicants note that Figure 4 provides

additional homology data for a range of other sequences, including human potassium channel K+Hnov27 protein human potassium channel K+Hnov28 protein and human KIAA 1 3 1 7 proteins as well as for several *C. elegans* and *Drosophila* sequences. This argument has been fully considered but is not found persuasive. The Office Actions have taken into consideration all of the homology data presented in the application (see especially page 8 of the 11 November Office Action). If the Office Actions have emphasized the low homology with Maxi-K potassium channel it is likely because it is the only homologous protein that has an established function. As pointed out previously, "[t]he prior art teaches K+Hnov27 and K+Hnov28 proteins, which are predicted to function as modulatory subunits for a K^+ channel although no empirical evidence is provided to support this supposition" and "the prior art teaches a human hypothetical protein KIAA1317, *D. melanogaster* CG10830 and CG10465 proteins, *C. elegans* protein VM106R.1, the functions of which are unknown as evidenced by the TrEMBL reports" (11 November Office Action, page 8).

In response to the Examiner's contention that the specification lacks any teaching that would enable one of ordinary skill in the art to use the claimed invention without first engaging in undue experimentation, Applicant again submits that the claims are enabled because the specification provides general guidance on the use of polynucleotides cloning expressing a polypeptides, carrying out bioinformatics operations, identifying the presence of an abnormally high or low level of expressing a polypeptide encoded by the claimed sequences, and tissue profiling. Applicant asserts that the claimed sequences encode a potassium channel beta subunit, and, therefore, those of ordinary skill in the art would recognize the merits of the applications

disclosed in the specification. This argument is not persuasive because as pointed out in previous office actions, "Applicant has placed on the shoulders of the skilled artisan seeking to use the claimed polynucleotides the burden of: first, identifying the activity of the polynucleotides or encoded polypeptides; next, correlating that activity with a disease state; and finally, developing diagnostics or therapeutics from the claimed polypeptides" (11 November Office Action, page 7). The specification discloses a nucleic acid encoding a polypeptide having very low homology to any polypeptide of established function and teaches the skilled artisan that the polynucleotide can be used in assays and to treat diseases. However, the disclosure provides no suggestion of what the assays might be used for other than to further characterize the claimed nucleic acid or to diagnose or treat some unspecified disease. As pointed out previously, "in the absence of a known function for the claimed invention, the disclosure does not provide a patentable utility other than as a diagnostic or therapeutic. For reasons of record, the skilled artisan would not be able to use the claimed invention for that purpose without first engaging in undue experimentation" (3 June Office Action, page 8).

Applicant contends that the use of data generated in accordance with the cited examples would be apparent to those of ordinary skill in the art and would be of use in the same way such data is useful with regard to other proteins. Applicant suggests that transgenic animals could be used to evaluate a candidate therapeutics, antibodies could be used in antibody-based therapies, immunophenotyping procedures and protein purification operations and the ability to make a determination as to the presence or absence of a mutation can contribute to a method of a diagnosing conditions associated with potassium channels and potassium channel disorders, such as myokymia, long QT syndrome, epilepsy and Bartter's syndrome. However, this argument fails

to appreciate the amount of experimentation that would be required to use the claimed nucleic acids for any of these purposes even if one were to assume that the nucleic acid has the asserted function. In order to use a transgenic animal to evaluate candidate therapeutics, the skilled artisan would have to first establish the animal as a model for a disease; in order to use an antibody as a therapeutic, the skilled artisan would have to first identify a disease that could be treated and develop a therapeutic approach; in order to use a molecule as a diagnostic, the skilled artisan would have to establish some measurable property of the nucleic acid or protein as a reliable marker for a disease state. The instant specification provides only tenuous evidence that the disclosed nucleic acid might encode a part of a potassium channel and suggests some diseases in which potassium channel dysfunction might play a role. Given no more than this, it would plainly require undue experimentation to use the claimed invention for the purposes suggested by Applicant.

Next, Applicant argues that the data presented in Example 6 support Applicant's claim to a method of diagnosis because extrapolating functional data from a polynucleotide encoding a protein having only 24% identity and also from data obtained in insect cells to the mammalian organism relies on established scientific principals. This argument is not found persuasive because it again fails to appreciate the tremendous amount of experimentation required to establish an insect comprising a mutation in a gene having no known function as a model for human inflammatory disease caused by a mammalian protein having very limited homology to the insect protein. Furthermore, Applicant's argument does not address the scope of the claim. As pointed out in the 3 June Office Action, "Applicant is claiming a method of diagnosing any

disease that might be associated with a mutation in the disclosed polynucleotide. Clearly the teachings of Example 6 do not support such breadth" (page 9).

Finally Applicant submits that a CLUSTALW alignment for determining percent identity has utility beyond investigation of the claimed invention because the recitation of the precise algorithm by which a percent identity can be determined, coupled with the discussion of the use the algorithm presented specification, provides all guidance that would be useful to one of ordinary skill in the art when practicing claim 38 as claimed. This argument is not found persuasive because Applicant does not indicate what the skilled artisan would do with the CLUSTALW alignment other than investigate the claimed invention.

For reasons of record and herein above, the teachings of the disclosure do not enable the skilled artisan to use the instant claimed invention for the purposes indicated in the specification without first engage in undue experimentation. Therefore, the claims are not enabled by the disclosure.

New Grounds

Double Patenting

Applicant is advised that should claim 35 be found allowable, claim 39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20-41 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

In order to comply with the utility requirement of 35 U.S.C. § 101, claimed subject matter must be supported by a disclosure of a specific, substantial and credible utility or by a well-established utility. The instant claims are directed to a nucleic acid molecule encoding a polypeptide which is asserted to have the function of a potassium channel beta subunit based on homology of the protein with other proteins described in the art. Throughout, the specification teaches that the claimed polynucleotide has direct utility as either a therapeutic or diagnostic agent or in the production, identification or isolation of other molecules having therapeutic or diagnostic utility. The specification also provides a laundry list of diseases that might be treated using the claimed invention or products made using the claimed invention (see beginning on page 20 and continued through page 32). However, the list of diseases is highly divergent and includes treatment of viral and bacterial infections, diarrhea, constipation, cystic fibrosis, metabolic diseases and disorders, premature puberty, cancer and Alzheimer's disease. The specification provides no direct evidence that the invention can be used as a therapeutic or diagnostic for any of the listed diseases, but instead speculates that the invention might be useful for treatment or diagnosis of one or more of the listed conditions based on possible function as a component of a potassium channel (see, e.g., page 24, paragraph 3) or as a secreted factor that

influences the differentiation or behavior of blood cells (see, e.g., page 27, lines 31-33). Although the specification teaches that the claimed invention can be used as a therapeutic or diagnostic, it fails to specify a disease that can be diagnosed or treated using the claimed nucleic acid. Therefore, the specification fails to provide a specific utility for the invention.

Furthermore, the asserted utility for the claimed invention is primarily based on the assumption that the nucleic acid encodes a MaxiK potassium channel beta subunit, which is in turn based on some limited homology with proteins known in the art. However, the art generally acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000) *Trends Biotechnol.* 18:34-39 teaches that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating specific details of protein function (see Box 2, page 36). Similarly, Bork (2000) *Genome Res.* 10:398-400 teaches that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially page 399). Smith *et al.* (1997) *Nature Biotechnol.* 15:1222-1223 teaches, "[t]ypical database searching methods are valuable for finding evolutionarily related proteins, but if there are only about 1000 major superfamilies in nature, then most homologs must have different molecular and cellular functions" (second column on page 132). These teaching demonstrate the unpredictability of assigning protein function based on structure alone.

In the instant case, the specification teaches that the claimed nucleic acid encodes a polypeptide sequence having 0% identity and 37.5% similarity to the MaxiK channel β-subunit protein, and identities of 24% to CG10465, 30% to K+Hnov27 and K+Hnov28, 31% to *C.*

elegans VM106R.1 protein, 51% with CG10830 and 60% with KIAA1317 (see especially Figure 4). The art teaches MaxiK channel β-subunit genes from rat, mouse, bovine and canine (for example, see Jiang *et al.* (1999) *Genomics* 55:57-67 and citations therein; already of record). Jiang *et al.* also teach that all five mammalian MaxiK β subunits have 191 amino acid residues of which 71% are identical in all species (see especially Fig. 5 and the caption thereto, and the final paragraph on page 63). The prior art teaches K+Hnov27 and K+Hnov28 proteins, which are predicted to function as modulatory subunits for a K^+ channel although no empirical evidence is provided to support this supposition (see Miller *et al.* (1999; WO 99/43696; already of record). The art also teaches a human hypothetical protein KIAA1317 (see NiceProt view of TrEMBL:Q9p2m9; already of record), *D. melanogaster* CG10830 (see NiceProt view of TrEMBL:Q9VDH3; already of record) and CG10465 proteins (see attached NiceProt view of TrEMBL:Q9V9F4; already of record), *C. elegans* protein VM106R.1 (see NiceProt view of TrEMBL:Q9XXA3; already of record), the functions of which are unknown as evidenced by the TrEMBL reports.

Thus, the specification asserts that the claimed polynucleotide encodes a MaxiK channel beta subunit based on very limited homology to a single protein having established function and homology with several other proteins which do not have an established function. With regard to the only protein having an established function, the prior art teaches that all mammalian proteins having the function of a MaxiK channel β-subunit are highly conserved, having 71% identity over the full length of the protein across species. Therefore, the skilled artisan would not predict that a mammalian protein having no identity to the MaxiK channel β-subunit would have the same, or even a closely related function. In the case of predicting the function of a polypeptide

based on similarity to proteins having unknown function, even if, for the sake of argument, the skilled artisan could predict with a high degree of certainty that the structurally related proteins had the same function, the function of the proteins remains unknown. Further, in the case of the proteins having less than 50% identity, the art cited above teaches that a related function would not be expected unless it could be established that the proteins comprised regions of high identity that could be correlated with a known function. Given the unconfirmed nature of the asserted function, and because the asserted utility for the claimed nucleic acid is based on the predicted function, one skilled in the art would have to perform additional experimentation to identify and/or reasonably confirm the functional characteristics of the claimed invention. Furthermore, once the function of the claimed invention was established, the skilled artisan would have to perform additional experiments to identify a condition that could be treated or diagnosed according to the teachings in the specification, and still more experiments to establish that the invention could actually be used as a therapeutic or diagnostic. Given that additional experimentation is clearly required to reasonably establish that the claimed invention could be used for the purposes set forth in the specification, the asserted utility would not be considered substantial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-41 are further rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to a polynucleotide comprising a segment encoding a defined portion of the polypeptide set forth as SEQ ID NO: 2. However, the claims from which claims 24 and 26 depend are directed to a nucleic acid consisting of a polynucleotide that encodes the same portion of SEQ ID NO: 2. Because claims 24 and 26 use open language in claiming the polynucleotide, the claims appear to be broader in scope than the claims from which they depend. Amending the claims to recite "consisting of" rather than "comprising" would be remedial.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms